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## ORIGINAL ARTICLE

# Obstructive sleep apnea in patients with rheumatoid arthritis: Correlation with disease activity and pulmonary function tests



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### KEYWORDS

Rheumatoid arthritis;  
 Obstructive sleep apnea;  
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 Pulmonary function tests

**Abstract** *Aim of the work:* To assess obstructive sleep apnea (OSA) as one of the common primary sleep disorders in patients with rheumatoid arthritis (RA) and study its correlation to disease activity and pulmonary function tests.

*Patients and methods:* This study included 30 female patients with RA who fulfilled the American College of Rheumatology/European league against rheumatism classification criteria. All the patients were subjected to full medical history, thorough clinical examination with evaluation of the disease activity using disease activity score-28 (DAS28), laboratory assessment of highly sensitive C-reactive protein (hsCRP), pulmonary function tests (PFTs) (FVC, FEV1 and FEV1/FVC) and one night polysomnography at the sleep laboratory.

*Results:* Polysomnographic data revealed OSA in 14 RA patients (46.7%). Patients with OSA showed longer disease duration ( $7.0 \pm 1.94$  years), higher BMI ( $30.8 \pm 2.48$ ), hsCRP level ( $6.7 \pm 0.6$  mg/L) and DAS28 ( $4.9 \pm 1.85$ ) than patients with no OSA ( $4.0 \pm 1.72$  years,  $20.3 \pm 1.55$ ,  $4.9 \pm 0.3$  mg/L and  $3.7 \pm 1.28$  respectively). There was non-significant difference between both groups regarding the PFTs ( $p > 0.05$ ). The study showed a significant correlation between AHI (apnea-hypopnea index) and BMI, hsCRP and DAS28 ( $r = 0.45$ ,  $0.43$  and  $0.51$ , respectively) ( $p < 0.05$ ). No significant correlation was detected between AHI and PFTs.

*Conclusion:* Obstructive sleep apnea is commonly associated with RA patients; these findings possibly suggest common underlying pathological mechanisms which may be linked to chronic

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inflammation. Co-existence of OSA in RA patients may influence the disease activity and the level of circulating inflammatory markers. Considering diagnosis and treatment of this sleep disorder in RA patients may help in improved clinical care, better prognosis and avoid rheumatoid-associated morbidities.

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## 1. Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease that is characterized by joint pain and swelling and can lead to disability and functional limitations [1,2]. In addition, more than half of patients with RA report sleep disturbance, a rate of prevalence that is 2–3 times greater than that found in the general population [3]. Such disturbed sleep may be due to pain, depression, lack of exercise, or corticosteroid usage [4].

Cross-sectional studies have found that sleep disturbance correlates with greater pain and disease activity [5]. It is often thought that difficulties with sleep are due to RA-related pain. However, sleep disturbance and pain may be bidirectionally related [6]. Sleep dysfunction and primary sleep disorders are increasingly recognized in people with RA [7]. The morbidity and mortality which may be associated with untreated sleep disorders, particularly obstructive sleep apnea (OSA), raise the priority of this aspect of patient care [8].

Obstructive sleep apnea (OSA) is a significant public health concern and contributes to increased cardiovascular morbidity and mortality [9]. It is defined by the American Academy of Sleep Medicine [10] as repetitive episodes of upper airway obstruction occurring during sleep and usually associated with a reduction in oxygen saturation [11]. Symptoms of concern include sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, insomnia, waking up breath holding, gasping or choking and loud snoring [12].

Diagnosis of obstructive sleep apnea can be indicated by symptomatology and the presence of known risk factors as increasing age, obesity and large neck circumference, although OSA can occur in individuals with none of these risk factors [13]. Also a number of tools and methods are available for the assessment of sleep health as self-reported questionnaire instruments [14]. However, the gold standard for diagnosis of OSA is the overnight polysomnography (PSG) [15].

The aim of the work was to assess obstructive sleep apnea (OSA) as one of common primary sleep disorders in patients with rheumatoid arthritis (RA) and study its correlation to disease activity and pulmonary function tests.

## 2. Patients and methods

The present study is a cross sectional one that included 30 female patients with RA, fulfilling the American College of Rheumatology/European league against rheumatism (ACR/EULAR) criteria for classification of RA [16]. They were selected from patients attending the Rheumatology and Rehabilitation outpatient clinic in Ain Shams University Hospitals (ASUH).

All the patients were on a stable disease-modifying drug regimen for three months prior to study entry. The study was approved by the local ethics committee and written

consent was obtained from all patients after a full explanation of the study.

### 2.1. Exclusion criteria

- Patients on anti-tumor necrosis factor (TNF) or corticosteroid therapy.
- Patients on sedative or hypnotic drugs or with history of withdrawal of stimulants as coffee or tobacco.
- Patients with abnormalities in soft palate or upper airway.
- Pregnancy.

### 2.2. Clinical assessment

- Full history taking was performed laying stress on disease duration and symptoms suggestive of OSA e.g. day-time sleep, somnolence, morning headache, fatigue, waking up, breath holding, gasping or choking and loud snoring.
- Local examination of the chest, ear, nose and throat was carried-out.
- The BMI ( $\text{kg}/\text{m}^2$ ) was determined by weight (kg) and height (m) (Quelet index).
- The disease activity was assessed using disease activity score 28 (DAS28) [17]. Patients with DAS28 score  $\leq 2.6$  were considered in remission [18].

### 2.3. Laboratory assessment

- Complete blood picture was assessed using coulter counter.
- Rheumatoid factor (RF) was evaluated by enzyme-linked immunosorbent assay (ELISA).
- Erythrocyte sedimentation rate (ESR) was determined using Westergren Blot method.
- Highly sensitive C-reactive protein (hsCRP) concentration was measured using a latex-particle enhanced turbidimetric immunoassay [19]. Samples of peripheral venous blood were collected and stored at  $-80^\circ\text{C}$  until the time of assay.

### 2.4. Pulmonary function tests

The tests were done in the pulmonary laboratory. The best of 3 measures obtained while the patient is breathing room air by flow volume spirometry (Flow mate model 2500) were used to calculate the following parameters:

- Forced vital capacity (FVC): amount of air that can be forcefully expelled from maximally inflated lung.
- Forced expiratory volume in 1st second (FEV-1): Volume of air expelled during the first second of FVC.
- Ratio of FEV-1 to FVC (FEV-1/FVC).

### 2.5. Polysomnography (PSG) (overnight sleep test)

The test was done in sleep laboratory in chest department in ASUH using the Somnomedic (Germany) system. The patient arrived about two hours before bed time without having made any changes in daily habits. The PSG consisted of 14 channel continuous polygraphic recording from surface leads for 2 electro-encephalography, 2 electro-oculography, chin electro-myography, electro-cardiography, sensors for nasal airflow (thermistor), tracheal sounds (microphone), thoracic and abdominal respiratory effort (piezo-electric), finger pulse oximeter, leg movements, body position and light.

Data obtained from this study were

- Apnea index (AI): Complete cessation of airflow breathing at the nostrils and mouth for at least 10 s or longer.
- Hypopnea index (HI): Decrease in rate and depth of breathing by 50% for 10 s or longer.
- Apnea-hypopnea index (AHI): Average number of apnea and hypopnea per hour of sleep. OSA is diagnosed if AHI is 5 or more [20].

Statistical analysis was done using 'Statistical Package for Social Science (SPSS) program version 21 (SPSS Inc., Chicago, IL, USA). Data were expressed as Mean  $\pm$  SD for quantitative parametric measures. Comparison between two independent mean groups for parametric data was performed using Student's *t*-test. Pearson correlation coefficient (*r*) was used to test correlation between two quantitative variables. In all tests if *p* value  $> 0.05$ : non-significant, if  $< 0.05$ : significant and if  $< 0.001$ : highly significant.

### 3. Results

This study included 30 female patients with RA; their ages ranged from 30 to 50 years (mean  $40.33 \pm 6.22$ ). The disease duration ranged from 3–12 years (mean  $6.0 \pm 2.82$ ). BMI of the patients ranged from 18 to 35 kg/m<sup>2</sup> (mean  $23.8 \pm 5.31$ ). Evaluation of disease activity by DAS28 ranged from 1.58 to 5.4 (mean  $3.16 \pm 1.01$ ) (Table 1).

Twelve of our patients (40%) had symptoms of OSA. As regards, laboratory assessment, RF was positive in 13 patients (43.3%). ESR ranged from 35–110 mm/h (mean

$58.33 \pm 13.28$ ) and highly sensitive C-reactive protein (hsCRP) ranged from 3–8 mg/L (mean  $5.3 \pm 0.58$ ).

By using DAS28 for assessment of disease activity, there was 10 active patients (33.3%) with their DAS28  $> 2.6$  (mean  $4.26 \pm 0.58$ ). While the other 20 patients (66.7%) were inactive (mean  $1.88 \pm 0.40$ ). Abnormal pulmonary function tests, were detected in 10 patients (33.3%); all showed an obstructive pattern (FEV-1/FVC ratio  $< 80$ ), while 20 patients (66.6%) had normal PFTs.

Fourteen of our patients (46.7%) met the diagnostic criteria for diagnosis of OSA by polysomnography (AHI  $\geq 5$ ) while in the other 16 patients (53.3%) no evidence of OSA was recorded.

According to the results of polysomnography, the patients were divided into 2 groups, patients with OSA ( $n = 14$ ) and patients without OSA ( $n = 16$ ). Comparison between both groups showed that patients with OSA had longer disease duration (mean  $7.0 \pm 1.94$  years), higher BMI (mean  $30.8 \pm 2.48$ ) and higher values of hsCRP ( $6.7 \pm 0.6$  mg/L) than patients with no OSA (mean  $4.0 \pm 1.72$  years,  $20.3 \pm 1.55$  and  $4.9 \pm 0.3$  mg/L respectively) with a highly statistically significant difference ( $p < 0.001$ ). There was a non-significant difference between both groups as regards age, ESR or number of patients with positive RF ( $p > 0.05$ ) as shown in Table 2.

As regards pulmonary function tests, of the 10 patients with obstructive pattern, 5 patients having criteria of OSA constituting (35.7%) of the patients with OSA (5/14) while the other 5 patients with abnormal PFTs were in the group of patients without OSA (31.3%) (5/16). So, there was statistically a non-significant difference between patients with and without OSA as regards patients with abnormal PFTs ( $p > 0.05$ ) as shown in Table 2.

Of the 12 symptomatic patients, 66% (8/12) had OSA while 33% of the 18 patients with no sleep complaints (6/18) also had OSA. In our study, the mean of DAS28 in patients with OSA was  $4.9 \pm 1.85$ , with 7 active patients constituting 50% (7/14); while the mean DAS28 in patients without OSA was  $3.7 \pm 1.28$  with 3 active patients (3/16, 18.75%). So there was a statistically significant difference between both groups as regards mean of DAS28 and the number of active cases ( $p < 0.05$ ).

The study showed a statistical significant correlation between AHI and BMI, hsCRP and DAS28 ( $r = 0.45, 0.43$  and  $0.51$ , respectively  $p < 0.05$ ) as shown in Figs. 1–3; while

**Table 1** Age, disease duration, body mass index, pulmonary function tests and polysomnographic data for rheumatoid arthritis patients.

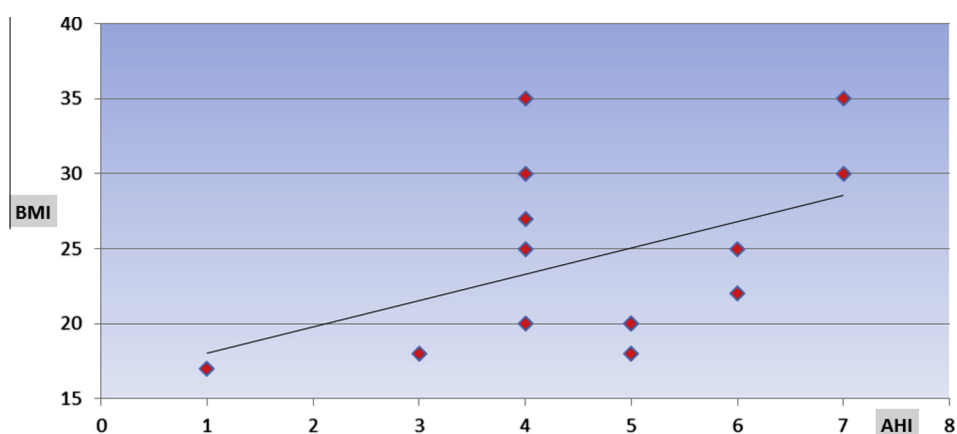
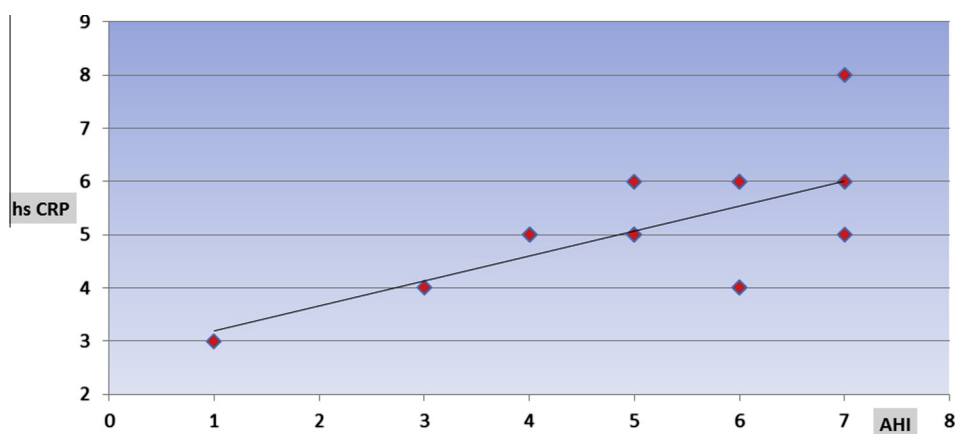
	Rheumatoid arthritis patients ( $n = 30$ ) range (min–max)	Mean $\pm$ SD
Age (years)	30–50	$40.33 \pm 6.22$
Disease duration (years)	3–12	$6 \pm 2.82$
Body mass index	18–35	$23.8 \pm 5.31$
<i>Pulmonary function tests:</i>		
Forced vital capacity (FVC)	56.9–81.1	$71.35 \pm 8.2$
FEV1	45.5–78.1	$62.5 \pm 8.75$
FEV-1/FVC	70–95.4	$83.35 \pm 4.71$
<i>Polysomnographic data:</i>		
Apnea hypopnea index	1–7	$3.66 \pm 1.77$

FEV-1, forced expiratory volume in first second.

**Table 2** Comparison between RA patients with and without OSA as regards demographic, clinical, laboratory and pulmonary function data.

	RA patients ( <i>n</i> = 30)		Sig
	With OSA ( <i>n</i> = 14)	Without OSA ( <i>n</i> = 16)	
Age (years)	41.2 ± 5.11	39.9 ± 6.6	<i>p</i> > 0.05
Disease duration (years)	7 ± 1.94	4.0 ± 1.72	<i>p</i> < 0.001 (HS)
Body mass index	30.8 ± 2.48	20.3 ± 1.55	<i>p</i> < 0.001 (HS)
ESR (mm/h)	54.34 ± 10.7	58.11 ± 12.9	<i>p</i> > 0.05
hsCRP (mg/L)	6.7 ± 0.6	4.9 ± 0.3	<i>p</i> < 0.001 (HS)
Active cases <i>N</i> (%)	7 (50)	3 (18.75)	<i>p</i> < 0.05 (S.)
Abnormal PFT <i>N</i> (%)	5 (35.7)	5 (31.3)	<i>p</i> > 0.05
Positive RF <i>N</i> (%)	6 (42.9)	7 (43.8)	<i>p</i> > 0.05

OSA, obstructive sleep apnea; ESR, erythrocyte sedimentation rate; hsCRP, highly sensitive C reactive protein; RF, rheumatoid factor; S, significant; HS, highly significant.

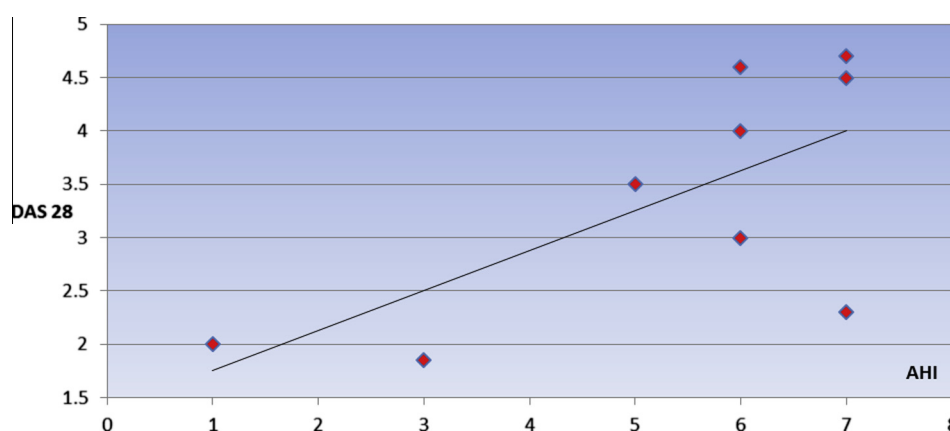
**Figure 1** Correlation between apnea-hypopnea index (AHI) and body mass index (BMI) in rheumatoid arthritis patients with obstructive sleep apnea (OSA).**Figure 2** Correlation between apnea-hypopnea index (AHI) and highly sensitive C reactive protein (hs CRP) in rheumatoid arthritis patients with obstructive sleep apnea (OSA).

no significant correlation was detected between AHI and FEV-1/FVC ratio ( $r = 0.102$ ,  $p > 0.05$ ).

#### 4. Discussion

Given that disturbed sleep is a well-documented symptom of RA, sleep is an important consideration in addressing their

health and well-being [21]. Most of our knowledge about sleep problems in RA depends on subjective self-report studies [22–24]. Except for few polysomnographic studies, there had been no large quantitative studies of OSA in RA [6,25,26]. So the aim of this work was to assess obstructive sleep apnea (OSA) as one of common primary sleep disorders in patients with rheumatoid arthritis (RA) and study its correlation to disease activity and pulmonary function tests.



**Figure 3** Correlation between apnea-hypopnea (AHI) and disease activity score 28 (DAS 28) in rheumatoid arthritis patients with obstructive sleep apnea (OSA).

In this study, OSA was diagnosed in 46.7% of RA patients. In 2003, Shimizu and his colleagues [25] conducted polysomnography evaluations in 96 consecutive Japanese RA patients (84% women). Remarkably, 53% of this cohort was found to have OSA by international standards of  $\text{AHI} \geq 5.0$ . They hypothesized that patients of Asian heritage have a higher rate of OSA, possibly due to cephalometric characteristics, but the expected prevalence in Japan would not be 53% [27]. Another pilot study conducted by Holman in 2004 [26] reported OSA in 45% of men with a connective tissue disease [RA, systemic lupus erythematosus (SLE), ankylosing spondylitis (AS) and psoriatic arthritis]. This is nearly in agreement to our results although all our cases were females. In a recent polysomnography evaluation of 25 RA patients, Gjevre and his colleagues [6] recorded higher percentage (68%) of RA patients with OSA. The high mean BMI of their study population ( $29.65 \pm 5.57$ ) may have contributed to the increased prevalence of OSA observed in their participants compared with other results.

These findings have implications regarding the potential contribution of OSA in rheumatologic-associated morbidities [28] in RA patients. OSA has been linked to inflammatory, coagulation, and endothelial changes, which can also be found in patients with RA and possibly suggest common underlying pathological mechanisms [29]. It has been suggested that the autonomic response to chronic OSA accounts for much of the increased cardiovascular disease (CVD) risk [30]. OSA is a potent and often forgotten cause of autonomic arousal [31]. Excessive sympathetic tone with noradrenergic activation during hypoxia and apnea may affect systemic vascular tone, metabolic and immunologic homeostasis through central and peripheral mechanisms. These autonomic abnormalities occur even when patients are awake and not hypoxic. An increased risk of sudden death in RA also raises concern for untreated OSA due to the impact of dysautonomia on arrhythmia [32].

In this study 33% of asymptomatic patients had OSA; this suggests that OSA may be under recognized in RA patients. There has been increasing recognition that OSA in women may differ symptomatically [33]. These differences may contribute to underestimation of OSA in women. As many rheumatological disorders affect a higher proportion of women than men, this concern may be relevant for clinical rheumatologists who have the best opportunity to identify such a concurrent disease within their patient populations. In

the study of Gjevre JA [6] higher percentage of asymptomatic RA patients (60%) had OSA. This can be explained by the higher percentage of OSA in their study compared to our study.

It is of interest that we recorded higher levels of hsCRP in RA patients with OSA. In consistent to our study, several works have demonstrated increased hsCRP values among OSA patients [34–36]. The postulated mechanism of the association between OSA and hsCRP is complex. OSA may have the effects of hypoxemia, reoxygenation, hypercapnia, and arousals which activate systemic inflammation with the production of CRP [37]. So co-existence of OSA in RA may influence the levels of circulating inflammatory markers and mediators in these patients [5]. However, more researches are needed also to elucidate these findings.

In this study we did not find a significant correlation between OSA and obstructive pattern diagnosed by PFTs in RA patients. The association between OSA and obstructive airway disease (OAD) has been investigated. However, so far the data available show conflicting results. Our results are in agreement with those of the study conducted by Sharma et al. [38]; while a negative association between PFTs and OSA was recorded in another study [39] on asthmatic patients. Some of the mechanisms that may link OSA with obstructive airway disease include increased parasympathetic tone during apnea, hypoxemia-related reflex bronchoconstriction, irritation of upper airway neural receptors, altered nocturnal neuro-hormonal secretion, and increased inflammatory mediators [40]. Corticosteroids may also contribute to OSA by causing upper airway myopathy [41]. However, Sharma and his colleagues [37] explained lack of association in their study that if there is a link between OSA and OAD, it appears not to be mediated via airway obstruction per se. It would be interesting to speculate other possible mechanistic links. The OAD group had higher BMI and larger neck circumference compared to general population and the link could be attributed to obesity [37]. Further investigation into all these mechanisms is clearly needed.

Disease activity, as represented by DAS28 was greater in RA patients with OSA. This is in agreement with the study of Gjevre and colleagues [6] who recorded a greater RA activity represented by RADA score in patients with OSA. These observations reinforce the concept of a relationship between



disease activity/functional status and perception of sleep health in patients with rheumatic diseases [14]. Also RA patients with OSA had longer disease duration and these data indicate that chronic illness plays an important role in disturbed sleep [6].

Interpretation of the present findings requires consideration of several limitations. First, the sample population was mainly composed of female patients consistent with the increased prevalence of RA in females. Hence, conclusions about the generalizability of these findings to males cannot be made. Also, the sample size limited our ability to apply a regression analysis in order to identify independent predictors for specific PSG findings. Finally, we have not been able to compare sleep questionnaire outcomes and PSG findings. Indeed, additional analyses are needed to examine the associations between subjective and objective measures of sleep disturbance in RA patients.

It is not expected that rheumatologists would diagnose and treat OSA; however, many symptoms of, or risks for, OSA may be picked up during rheumatological review. A high index of suspicion may facilitate recognition of possible OSA. Utilization of a simple screening questionnaire for OSA or daytime somnolence may be of additional benefit. Referral to a dedicated sleep clinic for further diagnostic assessment and therapy as required would be appropriate [14]. Cost considerations, mobility restriction and pain may limit evaluation of OSA using in laboratory PSG in RA patients. However, It is important to emphasize that the alternative sleep logs/diaries and questionnaires that assess various aspects of sleep represent perceptive rather than objective sleep disturbance and may be better indicators of patient perception of sleep disturbance than reflecting true, quantitative sleep abnormalities [24].

So a study of OSA in patients with RA may offer additional insight into why these patients are more apt to develop CVD. Therefore, treatment for co-existing OSA in patients with RA may prove beneficial in terms of future cardiovascular and respiratory morbidity, as well as potentially improving measures of fatigue, pain and inflammatory markers [21]. More researches are needed also to elucidate the impact of OSA on measures of therapeutic response to RA therapies and to clarify if anti-TNF therapy alter sleep disturbance or if OSA contributes to poor response to anti-TNF therapy in RA patients [42,43].

In conclusion, OSA is commonly associated with patients with RA. These findings possibly suggest common underlying pathological mechanisms which may be linked to chronic inflammation. Co-existence of OSA in RA patients may influence the disease activity and the level of circulating inflammatory markers in these patients. Considering diagnosis and treatment of this sleep disorder in RA patients may help in improved clinical care, better prognosis and avoid rheumatoid-associated morbidities.

### Conflict of interest

None.

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